REMARKS/ARGUMENTS

Claims 1, 3-7 and 14-20 were pending in this application. All claims have been rejected. To expedite prosecution without acquiescing to the Examiner's arguments, Applicants have amended claim 1. Amended claim 1 covers complexes of formula Ia, where Z is a heterocyclic amine having at least two alkyl substituents. Amended claim 1 also covers complexes of formula Ib, where Z is a heterocyclic amine having at least one alkyl substituent. Applicants have also added new claims 21 and 22. The amendments and new claims 21-22 are supported in the Specification, and do not include new matter (see e.g., Examples 1-16). Thus, claims 1, 3-7 and 14-22 are pending in this application. Applicants reserve the right to prosecute broader claims in the future.

Claim Rejections under 35 U.S.C. § 102

Claims 1, 3-4, 6, 7, 15, 16, and 18-20 were rejected as allegedly being anticipated under 35 U.S.C. § 102(b) by Broomhead *et al.* (Chem Abstract 124: 248674). Applicants must respectfully disagree. As previously indicated, claim 1 has been amended to expedite prosecution without acquiescing to the Examiner's arguments. Applicants address the Examiner's rejection in view of the amended claims.

To anticipate, the reference must disclose each and every element of the claimed invention. The Broomhead reference fails to disclose each and every element of the claimed invention. Specifically, claim 1 covers a *cis*-platinum complex of formula Ia and Ib, where all the substituents in the Z moiety are alkyl. Furthermore, these compounds contain a single Pt(II) core, and are not linked to another Pt(II) via a bridging ligand.

Unlike the presently claimed invention, Broomhead describes a bridged-dinuclear Pt(II) complex, where the bridging ligand is a pyrazolylmethane linked to Pt(II). The Broomhead reference fails to describe compounds having formula Ia or Ib, where all the substituents in the Z moiety are alkyl. A skilled artisan would understand that a pyrazolymethane linked to Pt(II) is not an alkyl substituent. If the Examiner believes that "alkyl" includes such a complex, Applicants respectfully request the Examiner to furnish evidence of such. Otherwise, Applicants respectfully submit that a *prima facie* case of anticipation has not been made, and request that this rejection be

withdrawn.

Claims 1, 3-4, 6, 7, 15, 16, and 18-20 were also rejected under 35 U.S.C. § 102(b) as allegedly being anticipated by Muir *et al.* (Chem Abstract 108: 215259). Applicants must respectfully disagree. Applicants address the Examiner's rejection in view of the amended claims.

Unlike the presently claimed invention, the Muir reference describes a platinum complex, where the ligand is a methyl-substituted imidazole. The Muir reference fails to describe a *cis*-platinum complex of formula Ia, where Z is a substituted 5- or 6-membered heterocyclic amine having at least two alkyl substituents, and all substituents are alkyl. The Muir reference also fails to describe compounds having formula Ib. Because Muir *et al.* fail to describe each and every element of the presently claimed invention, this reference does not anticipate. Thus, Applicants respectfully request that this rejection be withdrawn.

Furthermore, claims 1, 3-4, 6, 7, 15, 16, and 18-20 have been rejected under 35 U.S.C. § 102(b) as allegedly being anticipated by Saudek, *et al.* (Chem Abstract 102: 124545). Applicants must respectfully disagree. Applicants address the Examiner's rejection in view of the amended claims.

Unlike the presently claimed invention, the Saudek reference teaches a Pt complex having a carboxylic acid and amine substituent on a pyrazole. The Saudek reference fails to describe compounds having formula Ia or Ib, where all the substituents in the Z moiety are alkyl substituents. A skilled artisan would understand that such a carboxylic acid/amine group is not an alkyl substituent. If the Examiner believes that "alkyl" includes such substituent, Applicants respectfully request the Examiner to furnish evidence of such. Otherwise it is respectfully submitted that a *prima facie* case of anticipation has not been made, and respectfully request that this rejection be withdrawn.

In addition, new claims 21 and 22 are not anticipated by the Broomhead, Muir or Saudek references. Specifically, none of these references teach compounds having formula Ia, where Z is a heterocyclic amine having at least one alkyl substituent coupled to the heterocycle at a position one atom removed from the coordination atom in the heterocycle. Thus, these claims are allowable in view of the prior art cited by the Examiner.

Claim Rejections under 35 U.S.C. § 103

Claims 1, 3-7 and 14-20 were rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over Murrer, *et al.* (US Patent 5,665,771), for reasons indicated in the previous office action. In the Final action mailed 06/07/2002, the Examiner admits that the Murrer reference does not teach the four heterocyclic amines in the present invention (See, Final Office Action, page 3). However, the Examiner states that the generic teaching of Murrer coupled with its specific showing of a 5- or 6-membered unsaturated heterocyclic amine would provide sufficient motivation to select the claimed compounds from the genus in Murrer. (Office Action dated 6/5/03, page 3). Furthermore, the Examiner states that although the claimed compounds have improved solubility, Applicants have not shown side by side that the claimed compounds are superior to the reference compounds in the treatment of cancer. Applicants must respectfully disagree.

A *prima facie* case of obviousness in a genus-species chemical composition situation requires that the prior art suggest *the claimed compounds* to a person of ordinary skill in the art. MPEP 2144.08 (quoting *Deuel*, 51 F.3d at 1557, emphasis in original). To find such motivation or suggestion, there should be a reasonable likelihood that the claimed invention would have the properties disclosed by the prior art teachings. MPEP 2144.08 (See e.g., *Vaeck*, 947 F.2d at 493). Furthermore, evidence that the claimed invention yields unexpectedly improved properties rebuts the presumption of obviousness. MPEP 2144.08 (quoting *Dillon*, 919 F.2d at 692-93). Applicants respectfully submit that the amended claims are non-obvious.

First, there is no motivation to modify the Murrer reference because as the Examiner admits, Murrer simply fails to teach the four heterocyclic amines in the present invention. The Murrer reference merely indicates that Z is an "unsaturated cyclic amine," and indicates pyridine as a preferred embodiment (see Murrer, column 1, lines 39-45). Furthermore, all of the examples in Murrer relate to complexes where Z is pyridine. Murrer is silent with regard to 5- or 6-membered aromatic rings containing two heteroatoms, let alone any teachings on pyrazoles, imidazoles, oxazoles and pyrazines as ligands. At best, the Examiner is applying an "obvious to try" rationale in support of an obviousness rejection, which is improper. See, MPEP 2144.09.

Second, there is no reasonable likelihood that the claimed invention would have the properties disclosed by the Murrer reference because different heterocylic aromatics possess different chemical properties, which consequently affect their reactivities. For example, pyrazoles, imidazoles, oxazoles, pyrazines, and pyridines have different basicities, as shown by their pKa values. As indicated below, pyrazine and oxazole are very, very weak bases. Pyrazole is a weaker base compared to pyridine, which is a weaker base compared to imidazole. In view of the different heterocyclic aromatic ligands, there is no reasonable likelihood that compounds having formula Ia or Ib, with Z as alkyl substituted pyrazoles, imidazoles, oxazoles or pyrazines would have the same properties as a complex having a pyridine ligand.

	pKa
Pyrazine	0.65
Oxazole	0.8
Pyrazole	2.49
Pyridine (Murrer patent)	5.23
Imidazole	6.99

Furthermore, as previously indicated, evidence that the claimed invention yields unexpectedly improved properties rebuts the presumption of obviousness. As previously indicated, the compounds of the present invention have greatly improved solubilities compared to *cis*-ammine(2-methylpyridine)-dichloro platinum II, described in the Murrer patent. For example, *cis*-ammine(2-methylpyridine)-dichloro platinum II has a solubility of 0.7 g/mL (see, Table 1). In contrast, (OC-6-43)-amminedichlorodihyroxo-(1-methylimidazole)platinum(IV), shown as Example 12 in Table 1, has a solubility greater than 1000 mg/mL. In general, the greater aqueous solubility of the complexes allows for an easier formulation and administration of the drug, which is particularly important for intravenous administration. Specifically, a higher aqueous solubility would allow for a higher drug dose to be intravenously administered in a smaller volume of saline.

Applicants have also compared the compounds of the present invention to *cis*-ammine(2-methylpyridine)-dichloro platinum II, described in the Murrer patent, in the treatment of cancer, contrary to the Examiner's assertions. Specifically, resistance factors were determined using the

same set of cell lines as in Murrer. (See, Table 1 and Table 2 on pages 14-17 of the specification). The lower the resistance factor, the greater the ability of the drug to overcome drug resistance in the cancer cell line.

As shown in Tables 1 and 2, the compounds of the present invention have a reduced resistance factor than *cis*-ammine(2-methylpyridine)-dichloroplatinum II. For example, the resistance factors for *cis*-ammine(2-methylpyridine)-dichloro platinum II and (SP-4-3)-amminedichloro(1,3,5-trimethylpyrazole)platinum(II), shown as Example 2 in Table 2, are about 5 and 2, respectively. Thus, (SP-4-3)-amminedichloro(1,3,5-trimethylpyrazole)platinum(II) of the present invention has a resistance factor that is at least a two-fold decrease compared to *cis*-ammine(2-methylpyridine)-dichloro platinum II of the Murrer patent.

In addition, new claims 21 and 22 are not obvious in view of the Murrer reference. Specifically, the Murrer reference neither suggests nor teaches compounds having formula Ia, where Z is a heterocyclic amine having at least one alkyl substituent coupled to the heterocycle at a position one atom removed from the coordination atom in the heterocycle. Thus, these claims are allowable.

Based on the above, it would not be obvious to choose the claimed invention from the Murrer reference. As no motivation has been provided to select the claimed species that are superior in solubility and the treatment of cancer from among Murrer's genus of complexes, a *prima facie* case of obviousness has not been established. Applicants therefore, respectfully request that this rejection be withdrawn.

In the unlikely event that the transmittal letter is separated from this request and the Patent Office determines that a fee is required, applicant petitions for any required relief including extensions of time and authorizes the Assistant Commissioner to charge the cost of such petitions and/or other fees due in connection with the filing of this document to **Deposit Account No. 03-1952**, referencing docket no. 391442004300. However, the Commissioner is not authorized to charge the cost of the issue fee to the Deposit Account.

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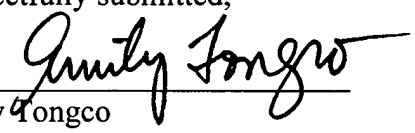
Respectfully submitted,

By 

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